Pickering, D. E. (1968). *Folia Primatol.* **8**, 169–179.
Rieser, J. W., Meyer, R. K., and Wolf, R. C. (1971). *Biol. Reprod.* **5**, 111–114.
Ruch. T. C. (1941). "Bibliographia Primatologica," Publ. No. 4, Historical Library, Yale Medical Library. Thomas, Springfield, Illinois.
Sade, D. S. (1964). *Folia Primatol.* **2**, 171–180.
Schane, H. P., Anzalone, A. J., and Potts, C. O. (1972). *Fert. Steril.* **23**, 745–750.
Shaw, S. T., Jr., Jiminez, J. M., Moyer, D. L., and Cihac, R. W. (1972). *Amer. J. Obstet. Gynecol.* **115**, 983–985.
Simpson, M. E. and van Wagenen, G. (1958). *Fert. Steril.* **9**, 386–399.
Simpson, M. E. and van Wagenen, G. (1962). *Fert. Steril.* **13**, 140–152.
Smith, P. E. (1942). *Endocrinology* **31**, 1–12.
Smith, P. E. (1944). *Yale J. Biol. Med.* **17**, 281–287.
Smith, P. E. (1954). *Endocrinology* **55**, 655–664.
Smith, P. E. (1955). *Endocrinology* **56**, 271–284.
Spies, H. G. and Niswender, G. D. (1972). *Endocrinology* **90**; 257–261.
Spies, H. G. and Niswender, G. D. (1973). *Endocrinology* **93**, 814–821.
Tullner, W. W. and Hertz, R. (1966). *Endocrinology* **78**, 1076–1078.
[redacted]enbergh, J. G. (1971). *Advan. Reprod. Physiol.* **5**, 103–118.
[redacted]Wagenen, G. (1945). *Endocrinology* **37**, 307–312.
v[redacted] Wagenen (1947). *Fed. Proc. Fed. Amer. Soc. Exp. Biol.* **6**, 219.
van Wagenen, G. (1949). Endocrinology **45**, 544–546.
van Wagenen, G. (1950). *In* "Care and Breeding of Laboratory Animals" (E. J. Farris, ed.), pp. 1–42. Wiley, New York.
van Wagenen, G. (1952). *Anat. Rec.* **112**, 436.
van Wagenen, G. and Catchpole, H. R. (1941). *Proc. Soc. Exp. Biol. Med.* **46**, 580–582.
van Wagenen, G. and Catchpole, H. R. (1956). *Amer. J. Phys. Anthropol.* **14**, 245–274.
van Wagenen, G. and Morse, A. H. (1940). *Endocrinology* **27**, 268–273.
van Wagenen, G. and Simpson, M. E. (1954). *Anat. Rec.* **118**, 231–252.
van Wagenen, G. and Simpson, M. E. (1957a). *Endocrinology* **61**, 316–318.
van Wagenen, G. and Simpson, M. E. (1957b). *Rev. Suisse Zool.* **64**, 809–817.
van Wagenen, G. and Simpson, M. E. (1965). "Embryology of the Ovary and Testis, *Homo sapiens* and *Macaca mulatta*." Yale Univ. Press, New Haven, Connecticut.
van Wagenen, G. and Simpson, M. E. (1973). "Postnatal Development of the Ovary and Induction of Ovulation in the Macaque." Yale Univ. Press, New Haven, Connecticut.
Waites, G. M. H. and Setchell, B. P. (1969). *Advan. Reprod. Physiol.* **4**, 1–63.
Walsh, E. L., Cuyler, W. K., and McCullagh, D. R. (1933). *Proc. Soc. Exp. Biol. Med.* **30**, 848–850.
[redacted]n, E. L., Cuyler, W. K., and McCullagh, D. R. (1934). *Amer. J. Physiol.* **107**, 508–512.
[redacted]<, R. F., Dierschke, D. J., Karsch, F. J., Yamaji, T., and Knobil, E., (1972). *Endocrinology* **91**, 1528–1530.
Weick, R. F., Dierschke, D. J., Karsch, F. J., Butler, W. R., Hotchkiss, J., and Knobil, E. (1973). *Endocrinology* **93**, 1140–1147.
Westman, A. (1929). *Acta Obstet. Gynecol. Scand.* **8**, 307–355.
Wislocki, G. B. (1933). *Anat. Rec.* **57**, 133–148.
Yamaji, T., Dierschke, D. J., Hotchkiss, J., Bhattacharya, A. N., Surve, A. H., and Knobil, E. (1971). *Endocrinology* **89**, 1034–1041.
Zuckerman, S. (1937). *Proc. Roy. Soc. (London).* **B123**, 441–456.

Exhibit C

5

*Embryology of the Rhesus Monkey**

Andrew G. Hendrickx and Roger H. Sawyer

Although the rhesus monkey (*Macaca mulatta*) has been used extensively in medical research for the past 70 years, embryological studies have received little attention. Prior to the report of Heuser and Streeter

* Unpublished data in this Chapter was supported by USPHS research grants RR00169 and HDNS08658 through the California Primate Research Center and School of Medicine, University of California, Davis.

(1941), which emphasized embryonic development during the first 3 weeks of pregnancy, most studies were concerned with events associated with ovulation or placentation (Hartman, 1932, 1933; Lewis and Hartman, 1933; Wislocki and Streeter, 1938). More recent studies have been directed toward defining the critical events during organogenesis as a preliminary step to experimental studies (Steffek *et al.*, 1968; Hendrickx, 1972a,b). The value of the rhesus monkey in the teratological evaluation of drugs which pose or may pose some threat to human pregnancies is well established (Wilson and Gavan, 1967; Wilson *et al.*, 1970; Wilson, 1972), although it should be recognized that the rhesus monkey is only one of eight species which are potentially useful in this field.

The purpose of this chapter is to present the available information on embryonic development for the rhesus monkey as well as some of the major developmental phases of placentation and fetal growth in order to provide a general account of prenatal development. The reader should bear in mind that in many instances the statements are based on limited observations and that much more research is necessary to understand how normal development proceeds and how it may be altered by environmental factors.

I. FERTILIZATION

Mastroianni and Brackett (1972) have recently presented the data which are known about fertilization and related events in primates. Fertilization, the fusion of male and female gametes forming a single cell, the zygote or embryo, begins with the entry of the sperm into the cytoplasm of the ovum and ends with the formation of the metaphase plate of the first cleavage division. The ovum is surrounded by cells from the ovary. The cells are organized into two layers; the loosely arranged outer layer of cells, known as the cumulus oophorus, are dispersed after the ovum enters the oviduct, while the more densely arranged corona radiata layer remains intact. The role of enzymes or spermatozoa in dispersing the peripheral cells surrounding the ovum has not as yet been explored; however, the acrosomal portion of the rhesus monkey spermatozoon has been shown to contain an enzyme complex consisting of hyaluronidase and a trypsinlike enzyme which is believed to be responsible for the ability of spermatozoon to penetrate the zona pellucida entering the perivitelline space (Stambaugh and Buckley, 1970). The trypsinlike acrosomal enzyme is located at a subcellular level in ejaculated rhesus monkey sperm and has been shown to exist in an active form prior to exposure of the spermatozoon to the female reproductive tract (Stambaugh and Buckley, 1972). From circumstantial evidence, it

is known that fertilization takes place in the oviduct, but it is not kno in what portion it occurs.

The number of sperm which are transported to the oviduct is relativ small despite the millions ejaculated into the vagina at copulati Marston and Kelly (1968) estimated that less than fifty spermato reached the oviduct following insemination directly into the uterus a after natural mating. This was done by counting the number of spe recovered in oviductal washings at specific times after inseminati Although there is no direct evidence that capacitation occurs, indir evidence suggests that rhesus monkey spermatozoa require capac tion before they are capable of fertilizing an ovum (Dukelow a Chernoff, 1969). Based on the time of sperm penetration, spermato require 3 to 4 hours for capacitation (Marston and Kelly, 1968). Af the spermatozoon penetrates the ovum, the latter finishes its seco maturation division and both the female and male pronuclei are form The fertile life of ova and spermatozoa is unknown.

Although the exact process by which the sperm penetrates the vi line (yolk) membrane has not been determined, it has been shown t the midpiece and tail are carried with the head into the ovum, m like many other mammalian forms (Marston and Kelly, 1968). Once spermatozoon has penetrated the zona pellucida and vitelline me brane and lies within the vitellus, the tail drops off, and the head swe forming the "male pronucleus" (Fig. 1). The second polar body proba is extruded from the ovum soon after the spermatozoon enters, a formation of the "female pronucleus" begins. Numerous nuclec are present in the pronuclei. In the next step of development, respective pronuclear membranes disappear, and the pronuclei no longer recognizable. Presumably, the pronuclei enter cleav division. O'Rahilly (1973) gives a more complete account of the chan that occur in the early stages of human development. The same crite are probably applicable to the study of rhesus monkey devel ment.

The time intervals between ovulation and fertilization, and fertili tion to the first cleavage division have not been thoroughly studied, Marston and Kelly (1968) recovered pronuclear stages within 6 ho after insemination, and Lewis and Hartman (1941) recovered a 2-c ovum from the oviduct 23 hours after mating. In the latter case, ovulati was believed to have occurred some hours before actual mating, a it was considered that the ovum may have been in the oviduct prio fertilization and was in an "overripe" condition. This may account fo slightly abnormal appearance and its failure to develop further in *in vi* culture.

II. CLEAVAGE

The fertilized ovum or embryo remains in the oviduct for 3 or 4 days before transfer to the uterus (Marston and Kelly, 1968; Lewis and Hartman, 1933, 1941). The timing of transfer from the oviducts to the uterus and the role of the utero–tubal junction in governing this transfer is not understood, although its importance has been demonstrated in several mammalian species. The normal course of cleavage has not been studied extensively in primates. No evidence is available for the first cleavage division, but the second cleavage division occurs at right angles to the first, the third approximately at right angles to the second. Cleavage divisions are not synchronized, so that both odd- and even-numbered cell stages may be found (Fig. 2).

A. Cleavage Rates

Information on cleavage rates is scanty indeed; only approximate estimates are available for rhesus monkey embryos (Lewis and Hartman, 1933, 1941). These estimates are based on the detection of ovulation by rectal bimanual palpation of the ovary at various intervals (Hartman, 1932, 1933) to confirm the duration of early cleavage stages from ovulation and the *in vitro* culture of the recovered ova. The cleavage stages were estimated as follows: 1-cell stage, 0–24 hours; 2-cell stage, 24–36 hours; 3- and 4-cell stages, 36–48 hours; 5- and 8-cell stages, 48–72 hours, and 9- and 16-cell stages, 72–96 hours after ovulation. Information on the transport of embryos down the oviduct is vague, but according to the studies cited above, the embryo enters the uterus at the 16-cell stage. The developmental stage at which the embryo reaches the uterus may be related to differences in either the rate of cleavage or in the rate of tubal transport.

B. Blastocyst

After the cleaving embryo (morula) enters the uterine cavity, it transforms into a blastocyst. The morula forms a cavity, the blastocoel, that enlarges, lining the zona pellucida with a layer of cells in the process. The polarity of the embryo is established at this time by the gathering of certain cells at one pole. These cells form the inner cell mass, or embryoblast, from which the embryo develops. The layer of epithelial cells on the inside of the zona pellucida comprises the trophoblast. The morula is converted into a blastocyst 5–6 days after ovulation and subsequent fertilization (Heuser and Streeter, 1941). The zona pellucida is shed 6 or 7 days after ovulation and prior to implantation (Fig. 3).

III. IMPLANTATION

Implantation occurs during the blastocyst stage of development a the zona pellucida is shed and the trophoblast comes in contact v the endometrium. Implantation in the rhesus monkey, as in ot primates, involves a sequence of integrated steps which have b reviewed recently by Blandau (1972). The blastocyst remains free in uterine lumen for 9 days before implantation occurs. The size and sh of the free blastocyst varies considerably (Heuser and Streeter, 1941), usually resembles a spherical mass. Some differentiation is occurrin the free blastocyst at days 8 and 9. The trophoblast is differentia into the polar trophoblast (i.e., in the region of the inner cell m which may become multilayered very early, and the single laye trophoblast cells which forms the continuous lining of the blastoc The inner cell mass gives rise to two types of cells—large, lightly stai cells (epiblast), and flattened epithelial cells that have delamin from the inner cell mass and constitute the endoderm (endobl Considerable change is seen in the cells comprising the various stituents in the 8- and 9-day blastocyst, as shown in the tabulation be

8-Day blastocyst	
Polar trophoblast cells	56
Cavity wall trophoblast cells	58
Epiblast cells (embryonic)	14
Endodermal epithelial cells	12
Total cells	140
9-Day blastocyst	
Polar trophoblast cells	95
Cavity wall trophoblast cells	224
Epiblast cells (embryonic)	32
Endodermal epithelial cells	24
Total cells	375

The trophoblast of the blastocyst is of special significance bec it is through the multifaceted functions of this membrane tha embryo remains viable and is secured to the maternal endomet (Blandau, 1972). The functions that have been ascribed to it incl (1) developing an attachment cone that initially anchors the blastc to the maternal endometrium; (2) acting as a selective membra control materials entering the blastocoel; (3) assisting in the esca the embryo from the zona pellucida; (4) transforming into the syn trophoblast at the appropriate time in development, and throu adhesiveness and cytolytic capabilities invading the endometrial str

and (5) producing and secreting both protein and steroid hormones and developing into a complex endocrine organ, the placenta.

The temporal relationship between escape of the blastocyst and its initial attachment to the endometrium for implantation has not been established for primates.

Precise timing and an intricate interplay of hormones on the endometrium are essential for successful embryonic attachment and implantation. This is even more critical in species, including the rhesus monkey and other primates, in which there is no delayed implantation. Some information is available for the hormonal requirements of implantation in the rhesus monkey. Meyer *et al.* (1968) demonstrated that implantation occurs in the presence of progesterone alone and in the absence of ovarian estrogen. Although ovarian estrogen is not required for implantation, the possibility that the adrenal cortex provides sufficient estrogen for implantation or the possibility that the uterus may have become sensitized by the ovarian estrogen at a stage early in pregnancy, before the ovaries were removed, cannot be overlooked.

With regards to the orientation of the blastocyst to the endometrium, the trophoblast adjacent to the inner cell mass is the first site of attachment (Figs. 4 and 5). Attachment is preceded by rapid proliferation of the trophoblast cells, as indicated by the difference in numbers of cells in 8- and 9-day blastocysts, and the formation of a syncytium in the trophoblast above the inner cell mass. Alterations in the endometrial epithelium are visible at very early stages of attachment of the blastocyst. The nuclei are deranged and the cytoplasm stains lightly, possibly indicative of beginning erosion and cytolysis (Blandau, 1972). According to Heuser and Streeter (1941), the trophoblast is probably active in the lysis of the uterine epithelium. During the initial attachment, the uterine epithelium immediately above the inner cell mass is disrupted. Invasion of the uterine stroma is accomplished on the tenth day of development, and the gap filled by the invading embryo is filled by the rapidly developing syncytium. The embryo collapses somewhat as it invades the endometrium. The surface epithelium and the necks of the glands proliferate on the outer boundaries of the embryo. There is no evidence of a decidual response in the uterine wall at day 10, or is there an indication of when definitive decidualization begins (Heuser and Streeter, 1941). The attachment or implantation of the rhesus monkey embryo is superficial, attaching itself to the endometrium and remaining partially within the uterine cavity. This is in contrast to the chimpanzee and human embryo, which are completely interstitial in their implantation.

IV. BILAMINAR DISC

Differentiation of the inner cell mass begins as early as day 9, at w time the inner cell mass and trophoblast are indistinct. By the tenth the inner cell mass is actively dividing, and the cells of the epiblas distinguishable from the angiogenic cells. The epiblast consists, fir irregularly arranged cuboidal cells which become pseudostrat columnar by day 11. It increases in size, but otherwise changes little about day 16, when the primitive streak first appears (Figs. 6 and 7). S endoderm cells are delaminated from the inner cell mass as the bl cyst is implanting; however, active proliferation occurs after attachi on days 10 and 11. From a few scattered cells the endoderm forms a definite layer beneath the epiblast. The cells of the endodermal are loosely arranged and cuboidal in shape, and do not bec organized into a plate until about day 16, at which time the polarity c embryo is established with the formation of the prochordal pla the cranial end, and the development of the body stalk at the ca end.

V. TRILAMINAR DISC

The caudal portion of the primitive streak develops very precocic between days 12 and 14 (Luckett, 1971). The caudal portion c primitive streak, which is quite inconspicuous at this stage, is consic to be the primary source of the extraembryonic mesoderm, althoug trophoblast may provide an additional contribution. The prir streak is readily observed in 16- and 17-day-old embryos (Fig. 7 a It appears as a proliferated area along the craniocaudal axis in the c region of the ectodermal plate. There are localized areas of diso ized cells along its entire length until the last segment is laid dowr primitive streak gives off embryonic mesoderm along its craniol margins and endodermal cells ventrally. The endodermal cells l with the primitive endoderm to form the gut endoderm. The r dermal cells cluster in their craniolateral movement and form the of Heuser, and initiate the development of the notochord. A blastc depression (primitive pit) forms in the older specimens as the ecto is elevated by the increased proliferation of cells.

The notochord appears by the nineteenth day as a short, mode thick column of cells extending cranially from the primitive stre the prochordal plate. It is quickly organized into a rodlike mass remains closely opposed to the endoderm and to the neural ectoderm at its cranial end. The notchordal canal, which forms a

communication between the amniotic cavity dorsally and the vitelline cavity ventrally, appears shortly after the notochord is formed and extends over its full length by the time the somites appear.

The prochordal plate, which along with the body stalk establishes the polarity of the embryo, appears early and remains as a distinct landmark until somite formation is underway. It marks the location of the buccopharyngeal membrane.

VI. ORGANOGENESIS

Studies concerning the development of organs and organ systems in the rhesus monkey are limited to the gonads (van Wagenen and Simpson, 1965) and the palate (Asling and van Wagenen, 1967; Steffek *et al.*, 1968). Although other organ systems have not been studied beyond establishing criteria for staging, there is little reason to believe they differ significantly in their development from other mammalian forms. The main structural changes during organogenesis are outlined in Figs. 1 through 23. Because the embryo develops at variable rates after fertilization, the stated days of gestational age must not be regarded as exclusive, but rather as modal. The timing of gestation has been reasonably accurate, because of the ability to identify the time of ovulation in a practical way. The gestational ages given in Figs. 1–23 are based on the actual palpation of the ruptured follicle following ovulation (Hartman, 1933), or by matings of only 2 hours duration (Hendrickx, 1972b). Staging of embryos by correlating external and internal form with age and size provides the criteria for determining the age of an embryo with an unknown history or calculating the degree of development at a particular stage in pregnancy for experimental purposes. Staging follows that originally proposed by Streeter (1942, 1945, 1948, 1951) for human embryos, but modifications presented by O'Rahilly (1972) have been included. The modifications include the designation "stage" as a replacement for "horizon," and Arabic numerals have replaced Roman numerals. Figures 1 to 23 are drawings of photographs of actual embryos which represent stages 1–23.

VII. COMPARISON TO THE HUMAN EMBRYO

Sufficient data are available to compare rhesus monkey and human embryos with respect to developmental stage, crown-rump length, and ovulation age (Fig. 24). Figure 24A shows that the mean line for human embryos is inclined considerably more horizontally compared with that compiled for the rhesus monkey. This indicates that the mean length for

the estimated ovulation age is greater in human embryos at early ages but falls behind at later ages. There is great similarity in the developmental stage in relation to crown-rump length in human and rhesus monkey embryos (Fig. 24B). A comparison of developmental stage with estimated ovulation age shows that human embryos are about 5 days older than rhesus monkey embryos for each developmental stage (Fig. 24C).

VIII. EXTRAEMBRYONIC MEMBRANES

The mode of development of the extraembryonic membranes has only been studied to a limited degree in the rhesus monkey. Figure 25 shows the difference in extraembryonic membrane relationships between *Galago* and higher forms such as the rhesus monkey.

A. Amnion

Amniogenesis begins on day 10 of development (Heuser and Streeter, 1941). At this time, a layer of amniogenic cells is clearly demarcated from the embryonic disc and is in the process of being delaminated from the trophoblastic wall. At the same time, fluid accumulates in the intercellular spaces between the amnion cells and the embryonic disc. The amniogenic cells become aligned into a single-layered membrane as they differentiate from the cytotrophoblast. By day 12, delamination of the amnion from the trophoblast is advanced, and a reticular network is laid down between them. Extraembryonic mesoderm occupies the reticular space, and by day 13 it forms the second layer of the amnion. From this point, the amnion expands (Figs. 6 and 7) at the expense of the exocoelomic space, and completes its reflections about the embryo and umbilical cord. In some instances, a secondary connection between the amnion and chorion exists, resulting in the formation of the amniotic duct passing from the caudal extremity of the amnion to open onto the surface of the trophoblast. Although it is clearly a secondary structure resulting from caudal prolongation of the amnion along the developing body stalk, it is common to many Old-World monkeys, apes, and man (Hill, 1932).

B. Allantois and Body Stalk

There are few details available on development of the allantois in the rhesus monkey; it remains rudimentary and plays no major role in

development. The allanto-enteric diverticulum quickly subdivides into allantois and cloaca, and the allantois extends about one-half the way into the body stalk. Its endodermal portion is slightly thicker than the lining of the vitelline sac.

The body stalk develops prior to the appearance of the primitive streak. It is sometimes described as having two parts—a short, cylindrical, distal part, continuous with the chorionic mesenchyme, and a longer, proximal part, attached to the amniotic ectoderm. The latter part forms the posterodorsal wall of the amniotic cavity. The body stalk consists first of extraembryonic mesoderm and is later reinforced by mesoderm from the primitive streak. By the time the somites begin to form, the mesenchyme has condensed to form a solid stalk containing umbilical vessels, and by the time somite formation is complete, the umbilical cord (body stalk) has rotated into a ventral position, the embryo is coiled around it, and the amnion sheathes its proximal surface. Angiogenesis probably occurs simultaneously in the yolk sac, body stalk, and chorion.

C. Yolk Sac

Yolk sac development in the rhesus monkey is believed to differ slightly from that in humans. In the human embryo, on day 9 of development, cells delaminate from the cytotrophoblast to form Heuser's membrane, which is continuous with the edges of the endoderm layer. Together with the endodermal layer they form the primary yolk sac (Langman, 1969). In the rhesus monkey, this membrane is formed by migration of the primary endoderm cells along the inside of the blastocyst cavity (Heuser and Streeter, 1941). Extraembryonic mesoderm is laid down between the trophoblast and primary yolk sac by day 12 in both species and, at about this time, endoderm cells begin to spread over the inside of Heuser's membrane. This process continues until the newly formed cells gradually line a new cavity, the definitive yolk sac. The definitive yolk sac is smaller than the primary yolk sac, and there is evidence that in both species, large portions of the definitive yolk sac are pinched off (Hertig *et al.*, 1956). The possibility exists that the definitive yolk sac develops by opening of the endodermal plate and the primitive yolk sac is pinched off in toto and, as a result, plays no role in the formation of the definitive yolk sac (Strauss, 1945; Starck, 1956). The yolk sac remains small until about day 17, when distension begins. Although it is regarded as a vestigial structure, it is not uncommon to see the vesicle on the surface of the placenta at term.

IX. PLACENTATION

A. Formation

Of the extraembryonic membranes, the chorion is exclusively involved in the formation of the placenta, except in prosimians, such as *Galago* sp., in which the allantois also plays a role in placentation. As the placenta forms, the chorion takes on two forms—the membranous chorion, which extends between the two placental discs, and the villous chorion which is anchored to the endometrium. The rhesus monkey, like the majority of New- and Old-World monkeys, has a bidiscoid placenta which consists of two separate placental discs—a primary disc, the first site of attachment at the embryonic pole, and a secondary disc at the abembryonic pole.

Development of the placenta can be divided into three stages (Wislocki and Streeter, 1938):

1. *THE PRELACUNAR STAGE (PERIOD OF TROPHOBLASTIC PLATE)*

This stage encompasses the ninth and tenth day of development and is characterized by the presence of a solid trophoblastic plate at the primary implantation site which invades and destroys the uterine epithelium at the point of blastocyst attachment. The maternal reaction is proliferation of the uterine epithelium and the uterine glands. In the older embryos of this stage, the only sign of a secondary placenta at the abembryonic pole is some slightly enlarged trophoblastic cells. Proliferation of the endometrial epithelium and the cells along the necks of the glands at the secondary site is equal to that seen at the primary site.

2. *THE STAGE OF TROPHOBLASTIC LACUNAE*

This stage extends from approximately the eleventh to the fifteenth day. The lacunae, formed by the differentiation of the trophoblastic plate into a reticulated mesh consisting of syncytial trophoblast, fill with maternal blood and proliferation of the uterine epithelium increases. In 11-day-old embryos, the trophoblast at the secondary implantation site begins to proliferate but does not attach to the already proliferated endometrial epithelium. By the 12th day of development, actual attachment occurs and invasion of the trophoblast into the endometrium begins (Fig. 26A,B).

3. *THE VILLOUS STAGE*

This stage extends from about the 15th to the 35th day and is characterized by the formation of the chorionic villi. The villi form by the

differentiation of the cytotrophoblastic cell columns and the transformation of part of the cytotrophoblast into mesenchyme and angioblasts which form the villi cores. Proliferation of the uterine epithelium ceases at the beginning of this period. The uterine epithelium is replaced at the fetal maternal border by the junctional zone. The fetal part of the border is converted into a typical trophoblastic shell by the fusion of the expanded ends of the cytotrophoblastic cell columns into a distinct plate (Fig. 26C,D). The formation of the villi in the secondary placenta follows the same pattern as in the primary placenta but is delayed by several days (Fig. 27A,B).

4. *DEFINITIVE PLACENTA*

Formation of the definitive placenta is essentially complete by day 35 of development (Fig. 27C). Minor changes occur, including: (a) intervillous connections from strands of syncytium, (b) increased branching and refinement of the villi with age, and (c) a reduction of the chorionic vessels on the placental surface and those connecting the secondary placenta to the primary placenta, so that a number of vessels connect the two discoidal placental masses. The outgrowth of the chorionic villi from the chorion is the primary means of increasing the surface of contact between maternal and fetal tissues. The distribution of villi is limited to two discs, the primary and secondary, hence, the term bidiscoid placenta (Fig. 27D). Within the disc, the villi are extremely long and have a complex branching pattern. The chorion remains intact over the fetal capillaries throughout gestation, but certain maternal tissues are broken down and disappear during placental formation and reduce the number of membranes or cell layers comprising the placental barrier. In the placenta of the rhesus monkey, the endometrial epithelium, the endometrial stroma, and the maternal capillary endothelium are all destroyed and maternal blood bathes the chorion (trophoblastic surface of villi) directly. At the ultrastructural level there are further differences in the trophoblast (Enders, 1965). The trophoblast of higher primates, including the rhesus monkey, consists of one layer, thus, it is classified as the hemomonochorial type (Luckett, 1970; Panigel, 1970), in contrast to the hemotrichorial type found in several laboratory species. A comparison of the specific structural differences in the rhesus monkey, baboon, and man is shown in Table I.

B. Circulation

The passage of materials between the mother and embryo (fetus) occurs within the placenta. In the process of development, their respective blood streams are brought into close proximity so that an efficient

TABLE I Comparison of the Main Placental Features of the Rhesus Monkey, Man, and Baboon[a]

Rhesus monkey	*Man*	*Baboon*
Implantation		
Superficial	Interstitial	Superficial (central)
No decidual reaction	Pronounced decidual reaction	Partial decidual reaction; developing somewhat more slowly than in man
Transitory epithelial plaque	No epithelial reaction	No epithelial reaction
Secondary placenta	No secondary placenta	No secondary placenta
Trophoblast		
Boundary between maternal and fetal tissues—straight	Boundary between maternal and fetal tissues—very irregular	Boundary between maternal and fetal tissues—straight
No penetration of myometrium by trophoblast	Penetration of inner third of myometrium by trophoblast	No penetration of myometrium by trophoblast
No trophoblastic wandering cells	Trophoblastic wandering cells prominent	No trophoblastic wandering cells
Arteries		
Intravascular cells very early—17th day	Intravascular cells later—peak at 12th week	Intravascular cells very early—16th day
Migration of intravascular cells in lumen only	Walls also traversed by intravascular cells	Intravascular cells in lumen only
Elastic tissue extending half-way up in endometrium	Little elastic tissue beyond myoendometrial junction	Elastic tissue extends well into endometrium
Multiple openings to intervillous space from single stems—infrequent	Multiple openings—common	Multiple openings—common

[a]From Houston (1969). *Amer. J. Anat.* **126**, 1–15.

interchange may take place. The structure of the fetal circulation within the placenta is dependent upon the configuration of the chorionic villi which contain the blood vessels (Ramsey and Harris, 1966; Harris and Ramsey, 1966). A composite drawing showing the structure and corresponding circulation of a hemochorial placenta is shown in Fig. 28. The first column represents the structure of the villous tree, and column two demonstrates the fetal circulation and how blood vessels pass through the villi. The first two columns further demonstrate that the villus is firmly attached to the basal plate with free-floating branches protruding into the intervillous space along the length of the main villous trunk. Each villous trunk carries both arterial vessels, which branch and extend into the smaller terminal villi, and venous vessels which return the blood through the same villous trunk. There are no

anastomoses between villi, or between the vascular channels within a villus.

The remaining three columns of Fig. 28 represent the placental circulation of the maternal blood. In the discoid, hemochorial placenta, there are no preformed channels for the passage of maternal blood; instead, the maternal blood enters at the base into the space between the villi. In the absence of preformed channels, the flow of maternal blood within the intervillous space is not strictly random. Because the blood pressure in the maternal vessels entering at the base of the placenta is much greater than in the intervillous space, the blood is driven toward the chorionic plate, as shown in column four. The loose, semiattached fronds of villi which are encountered along the course of the blood stream baffle the flow and direct some of the blood laterally. The force of the blood entering the intervillous space pushes blood out through the venous channels, which are also located in the basal plate. As a result, the circulatory pathway of the maternal blood is governed by the pressure it is under when it enters the intervillous space. The spurting pattern of maternal blood into the intervillous space varies with the contracted or relaxed state of the uterus. Contractions of the uterus occur throughout pregnancy and vary greatly in intensity. The degree of contraction governs the rate of flow.

X. FETAL PERIOD

In human embryology it is customary to refer to the conceptus as a fetus toward the end of the eighth week postconception, when major organogenesis is essentially completed. This custom is gradually becoming accepted in nonhuman primate embryology as well, and for the rhesus monkey the conceptus is referred to as a fetus by about day 45. The most conspicuous developmental process during the fetal period is physical growth. By the process of histogenesis, the individual organs, established as simple structures during organogenesis, are converted into more specialized ones with a primary function. Functional maturation of individual organs has received only limited attention (Rakic, 1974), although it is of major importance. Environmental factors which influence physical growth are the availability of nutrients through the maternal diet and placental transport. The endocrine balance and the absence of disease also contribute to the maternal physiological state and are of considerable importance to the normal growth of the fetus. Studies related to physical growth of the fetus are somewhat limited, but work has been done (Kerr *et al.*, 1969) to provide sufficient data on normal organ growth of the rhesus monkey fetus (Tables II, III, and IV).

TABLE II The Growth Rates of Fetal Organs of the Rhesus Monkey[a,b]

Organ	50–75 Days	75–100 Days	100–125 Days	125–150 Days	150–175 Days
Lungs	503.67	82.13	24.60	18.77	−13.60
Heart	317.65	101.55	46.10	21.76	13.49
Liver	447.53	89.85	23.93	23.46	2.80
Adrenals	318.72	44.57	15.51	14.04	60.02
Kidneys	572.13	139.74	26.97	9.37	10.04
Thyroid	—	105.52	31.23	32.72	20.07
Thymus	—	115.54	59.69	24.18	−20.92
Spleen	119.24	120.07	33.04	19.74	6.64
Brain	—	99.69	49.87	10.28	4.74
Placenta	73.02	24.86	7.21	17.79	9.77
Fetus	392.40	98.01	39.12	23.31	6.59

[a]Derived from change in mean weight of organs at each gestational age. Figures indicate value ±1 SD. Data in mg/gm/day.
[b]From Kerr *et al.* (1969). *Growth* **33**, 201–213.

TABLE III The Growth in Weight of Major Organs during Fetal Life of the Rhesus Monkey[a,b]

Organ	Gestational age (days) 50	75	100	125	150	175
Total body wt.	4.003 ±0.987	43.27 ±3.49	149.29 ±9.73	295.30 ±27.00	467.38 ±42.76	544.4 ±101.6
Placenta	21.23 ±6.59	59.99 ±12.23	97.27 ±14.66	114.82 ±21.28	165.88 ±33.82	206.40 ±49.52
Brain	—	5.26 ±0.64	18.36 ±1.15	41.25 ±3.57	51.85 ±3.04	58.00 ±5.97
Spleen	0.017	0.068 ±0.014	0.271 ±0.071	1.495 ±0.096	0.739 ±0.131	0.861 ±0.265
Thyroid	—	0.015 ±0.007	0.054 ±0.011	0.096 ±0.052	0.175 ±0.060	0.263 ±0.137
Kidneys	0.017 ±0.007	0.225 ±0.080	1.145 ±0.155	1.92 ±0.37	2.37 ±0.37	2.96 ±0.67
Adrenals	0.007 ±0.003	0.065 ±0.022	0.138 ±0.026	0.192 ±0.026	0.259 ±0.100	0.649 ±0.279
Liver	0.148 ±0.061	1.80 ±0.40	5.84 ±0.69	9.33 ±1.38	14.81 ±1.49	15.85 ±2.84
Heart	0.025 ±0.006	0.226 ±0.048	0.800 ±0.090	1.72 ±0.39	2.66 ±0.35	3.55 ±1.22
Lungs	0.097 ±0.041	1.32 ±0.20	4.01 ±0.88	6.48 ±1.42	9.53 ±1.27	6.29 ±0.99
Thymus	—	0.086 ±0.35	0.333 ±0.126	0.829 ±0.277	1.331 ±0.432	0.635 ±0.223

[a]Figures indicate mean weight ±1 SD. All data in gm.
[b]From Kerr *et al.* (1969). *Growth* **33**, 201–213.

TABLE IV The Relative Growth Rate of Fetal Organs of the Rhesus Monkey[a,b]

Organ	Gestational age (days)					
	50	*75*	*100*	*125*	*150*	*175*
Placenta	551.7 ±201.5	140.6 ±29.9	65.2 ±9.1	38.8 ±5.9	35.8 ±8.1	34.4 ±3.3
Brain	—	12.14 ±0.99	12.30 ±0.49	14.02 ±1.18	11.15 ±0.88	11.14 ±1.88
Spleen	0.70	0.16 ±0.03	0.18 ±0.05	0.17 ±0.03	0.16 ±0.02	1.6 ±0.04
Thyroid	—	0.034 ±0.016	0.036 ±0.008	0.033 ±0.019	0.037 ±0.010	0.047 ±0.020
Kidneys	0.536 ±0.061	0.587 ±0.164	0.765 ±0.071	0.620 ±0.118	0.507 ±0.038	0.548 ±0.102
Adrenals	0.233 ±0.039	0.151 ±0.055	0.093 ±0.017	0.064 ±0.012	0.055 ±0.021	0.113 ±0.037
Liver	4.05 ±1.27	4.14 ±0.71	3.90 ±0.25	3.16 ±0.31	3.19 ±0.30	2.93 ±0.35
Heart	0.657 ±0.137	0.525 ±0.083	0.543 ±0.030	0.581 ±0.101	0.561 ±0.043	0.646 ±0.147
Lungs	2.63 ±0.47	3.04 ±0.43	2.68 ±0.47	2.19 ±0.42	2.04 ±0.14	1.22 ±0.26
Thymus	—	0.201 ±0.093	0.224 ±0.092	0.280 ±0.082	0.283 ±0.080	0.118 ±0.035

[a] Figures indicate mean value ± 1 SD. Data given in percentage total body weight.
[b] From Kerr *et al.* (1969). *Growth* 33, 201–213.

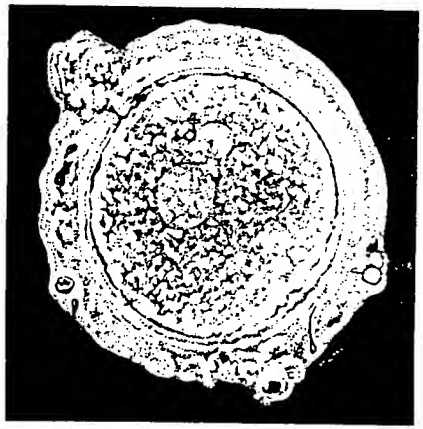

Fig. 1. Stage 1. 0–1.0 days post fertilization. One-celled ootid, male and female pronuclei present, corona radiata dispersed, sperm seen in zona pellucida, probably found in upper half of oviduct (after Suzuki and Mastroianni, 1968).

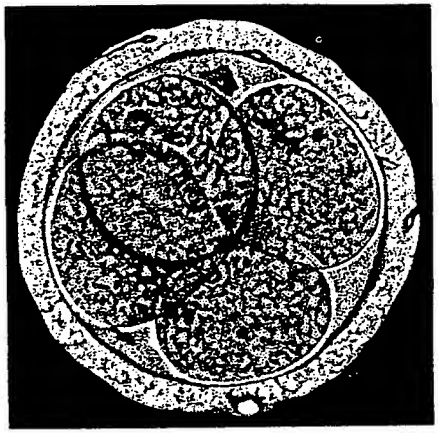

Fig. 2. Stage 2. 2–4 days. Segmentin blastomeres, 2- to 16-cell stages to morula zona pellucida persists, located in lowe half of oviduct and uterine cavity (afte Lewis and Hartman, 1941).

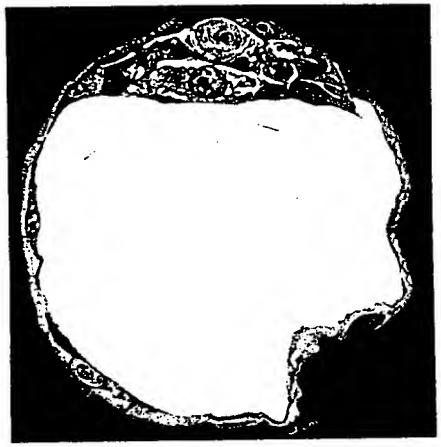

Fig. 3. Stage 3. 5–8 days. Free blast cyst with dilated blastocoel, inner ce mass well defined, no germ layer form tion, zona pellucida dissolving (sectio after Heuser and Streeter, 1941).

Fig. 4. Stage 4. 8–10 days. Attachir blastocyst, blastocoel distended, troph blast disrupting epithelium and impingir upon stroma, germ layer formation begin amniogenic cells appear (section, aft Heuser and Streeter, 1941).

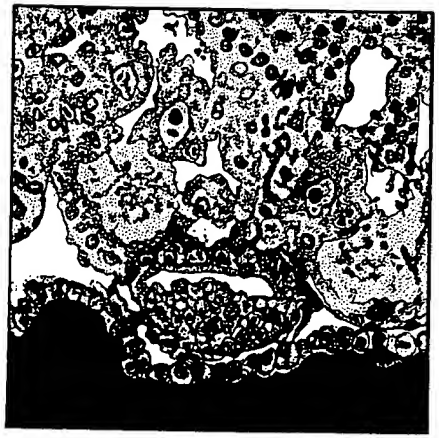

Fig. 5. Stage 5. 10–11 days. Trophoblast proliferating at embryonic pole, no villi, no maternal decidual response, amniotic cavity dilates, extraembryonic mesoderm proliferating (transverse section, after Heuser and Streeter, 1941).

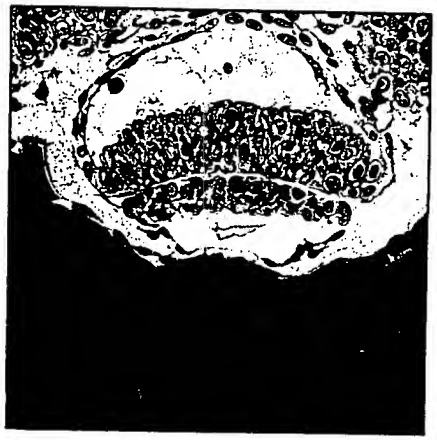

Fig. 6. Stage 6. 12–15 days. Primitive villi appear, yolk sac forms, bilaminar germ disc distinct, primitive streak begins to form, body stalk indicated (transverse section, after Heuser and Streeter, 1941).

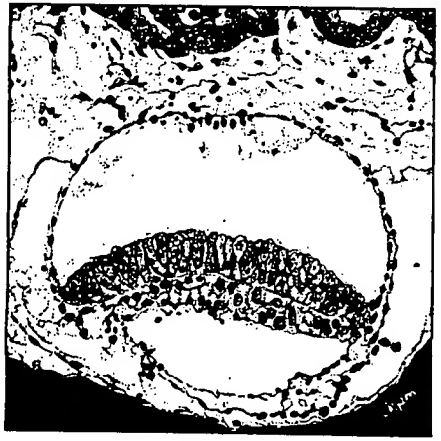

Fig. 7. Stage 7. 16–18 days. Branching villi appear, axis of embryonic disc determined by head process. Notochordal process appears, intraembryonic mesoderm begins to delaminate, primitive streak formed, angioblasts appear in the yolk sac and chorionic membrane (transverse section, after Heuser and Streeter, 1941).

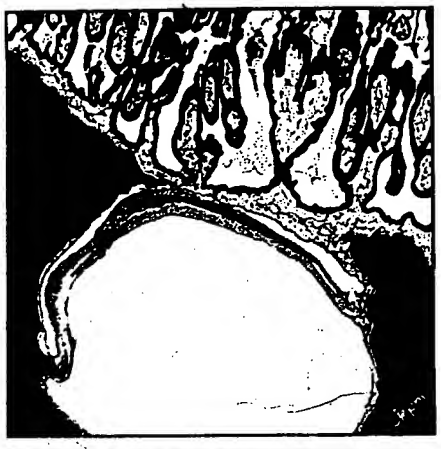

Fig. 8. Stage 8. 19–20 days. Embryonic disc elongating, definite body stalk present, primitive pit and neurenteric canal forming, primitive streak well established, intraembryonic mesoderm formed, neural plate appears (sagittal section, after Heuser and Streeter, 1941).

Fig. 9. Stage 9. 20–21 days; 0–3 paired somites. Obvious head fold, caudal fold appears, neural folds and goove distinct, foregut forms, primitive streak extends from cloacal membrane to neurenteric canal and occupies 1/3 to 1/4 the length of the embryo, notochord prominent, body stalk elongates (after Heuser and Streeter, 1941).

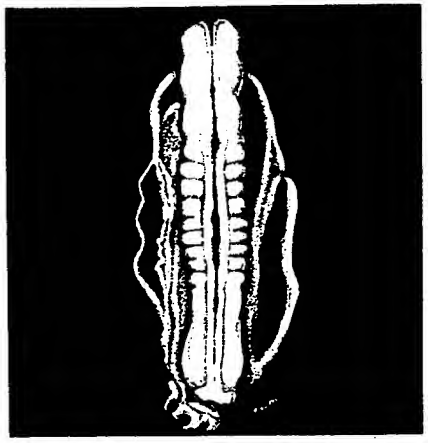

Fig. 10. Stage 10. 21–23 days; 4–12 somites. Neural folds begin fusing to form neural tube, optic primordia form, otic placodes readily detectable, 1st branchial arch (mandibular) evident, endocardial tubes fuse, 1st and 2nd aortic arches form, hindgut elongates (after Heuser and Streeter, 1941).

Fig. 11. Stage 11. 24–26 days; 2–3.5 mm; 13–20 paired somites. Cranial neuropore closes, optic vesicle evaginates, cranial nerves V, VII, VIII, IX, X, and XII appear, S-shaped heart with sinus venosus prominent, mandibular and hyoid arches well defined, 1st and 2nd pharyngeal pouches form, liver primordium forms, yolk stalk begins, body axis elongated and usually curved (after Heuser and Streeter, 1941).

Fig. 12. Stage 12. 27–28 days; 3–5 mm; 21–29 paired somites. Three branchial arches present, 3rd aortic arch appears, oropharyngeal membrane ruptures, optic vesicle contacts surface ectoderm, otic pit closing, appendicular ridge distinct and forelimb bud forming, yolk stalk formed, respiratory diverticulum evaginates, caudal neuropore closes, body axis C-shaped (after Heuser and Streeter, 1941).

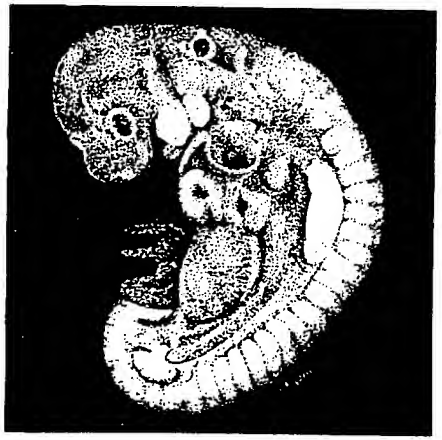

Fig. 13. Stage 13. 28–29 days; 4–6 mm. Four branchial arches present, maxillary process appears, lens placode evident, otocyst closed, olfactory placode appears, Rathke's pouch forms, hindlimb bud appears, thyroid primordium bilobed, gallbladder and dorsal pancreas appear, esophagus and trachea divide, stomach evident, mesonephric ducts join cloaca (after Heuser and Streeter, 1941).

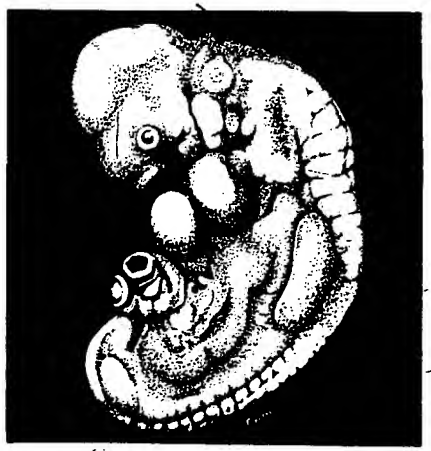

Fig. 14. Stage 14. 29–30 days; 5–8 mm. Optic cup and lens placode invaginate, endolymphatic duct forms, cervical sinus begins, Rathke's pouch prominent, pharyngeal pouches differentiated, lung buds elongate, ventral pancreas appears, metanephric bud forms.

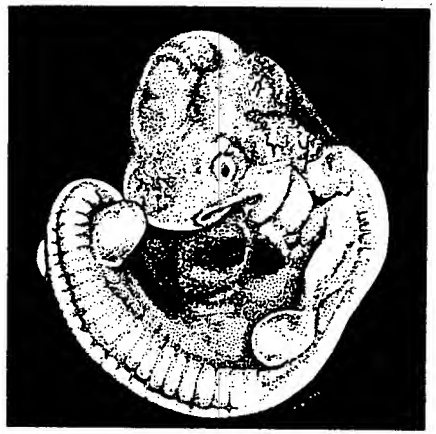

Fig. 15. Stage 15. 31–32 days; 6–9 mm. Lens vesicle closes, optic stalk prominent, pigment appears in retina, olfactory pits form, neurohypophysis appears, arm buds elongate and become flipper-shaped, leg buds elongate, cecal swelling appears.

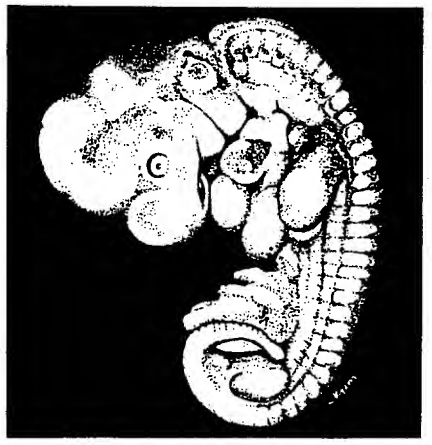

Fig. 16. Stage 16. 33–34 days; 8–11 mm. Pigment in retina prominent, neurohypophysis evaginates, cervical sinus closes, auditory hillocks appear, secondary bronchi appear, midgut loop herniated into umbilical cord, rotation of gut begins, hand plate evident, genital ridge appears, ureteric bud expands into renal pelvis.

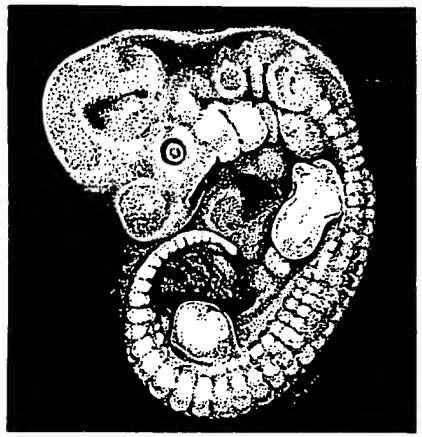

Fig. 17. Stage 17. 35–36 days; 10–12 mm. Nose and primary palate form, hand plate prominent and digital rays appear, foot plate appears, tertiary bronchi form, liver enlarges and biliary ducts appear, dorsal and ventral pancreas fuse, stomach rotates, Müllerian ducts appear, major calices of kidney appear.

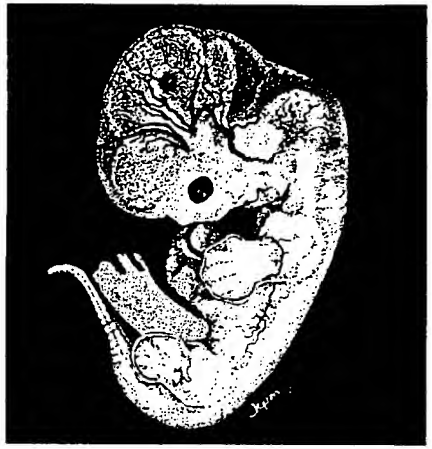

Fig. 18. Stage 18. 37–38 days; 12–16 mm. Facial primordia united, eyelids and eyes begin to move forward, auricular hillocks forming auricle, neurohypophysis begins to fold, cochlear duct L-shaped, semicircular ducts forming, digital rays of hand prominent, digital rays of foot appear, Müllerian duct prominent, minor calices formed, collecting tubules appear.

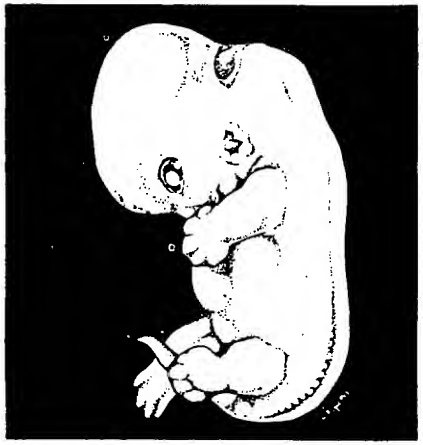

Fig. 19. Stage 19. 38–39 days; 15–19 mm. Semicircular ducts formed, cornea formed, cochlear duct J-shaped, buccon-asal membrane ruptures, auricular hillocks coalescing, secondary palate begins, submandibular gland appears, primordium of secretory tubules of kidney form, testis differentiates, forelimb rotating and interdigital notches present, cartilage cells appear in humerus, digital rays prominent in foot.

Fig. 20. Stage 20. 39–40 days; 17–20 mm. Optic nerve fibers reach brain, eyelids cover 1/5 of eye, palatine processes present beside tongue, palms directed caudally, primary branches appear in submandibular gland, ossification centers indicated by clearing of cartilage, interdigital notches present in foot, anal membrane ruptures.

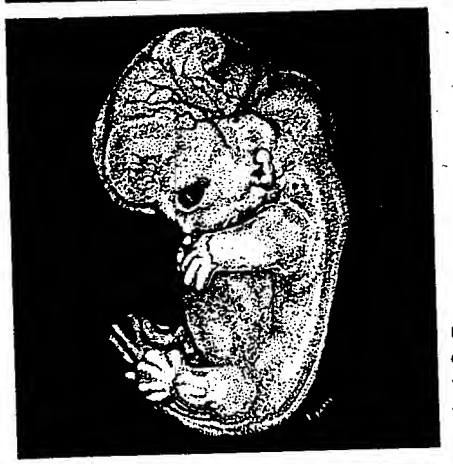

Fig. 21. Stage 21. 41–42 days; 19–23 mm. Three layers present in cornea, eyelid covers 1/4 of eye, cochlea completes one turn, collecting and secretory tubules fuse in kidney, osteoblasts appear in humerus.

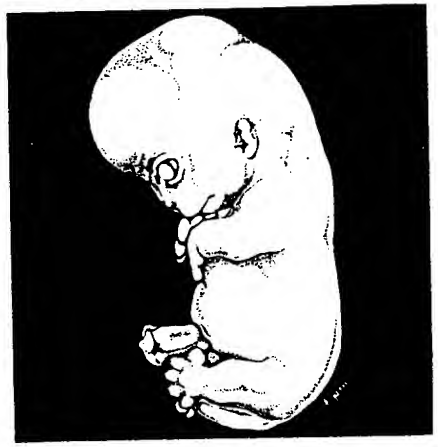

Fig. 22. Stage 22. 43–44 days; 22–26 mm. Eye rotated to front of face, eyelid covers 1/3 of eye, secondary branches appear in submandibular gland, palatine process rotated 45° medially, large glomeruli present, calcification begins in humerus, hindlimb rotating.

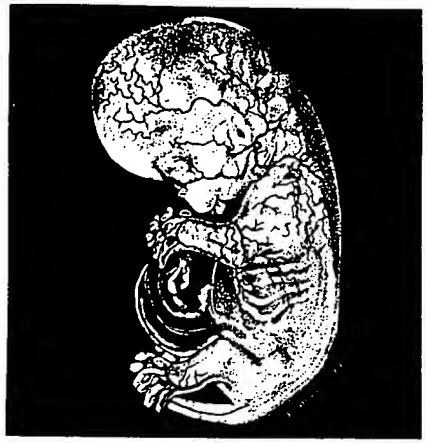

Fig. 23. Stage 23. 45–46 days; 25–30 mm. Head raised from chest, eyelids cover most or all of eye, hands overlap in front of face, soles of feet apposed, palatal closure begins, cochlea completes 2½ turns, tertiary branches appear in submandibular gland, midgut hernia withdrawing from umbilical cord, ovary recognizable.

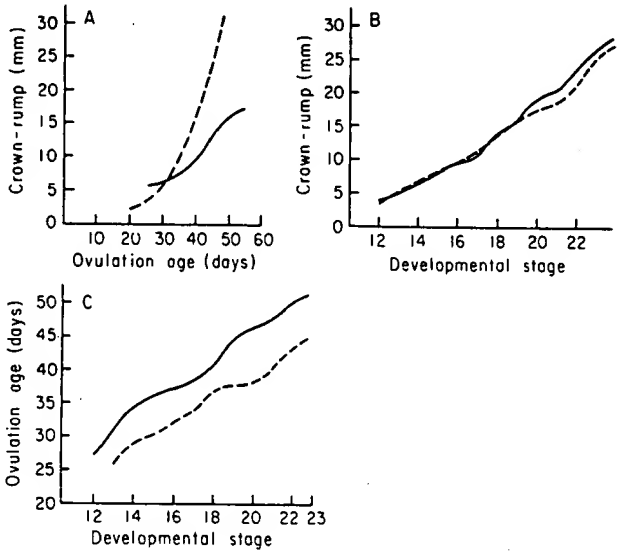

Fig. 24. (A) Correlation of estimated ovulation age and crown-rump length in rhesus monkey (– – –) and human embryos (——); (B) Correlation of developmental stage and crown-rump length in rhesus monkey and human embryos; (C) Correlation of developmental stage and ovulation age (data for man are taken from Nishimura *et al.*, 1968; data for the rhesus monkey are taken from Heuser and Streeter, 1941, and California Primate Research Center Collection).

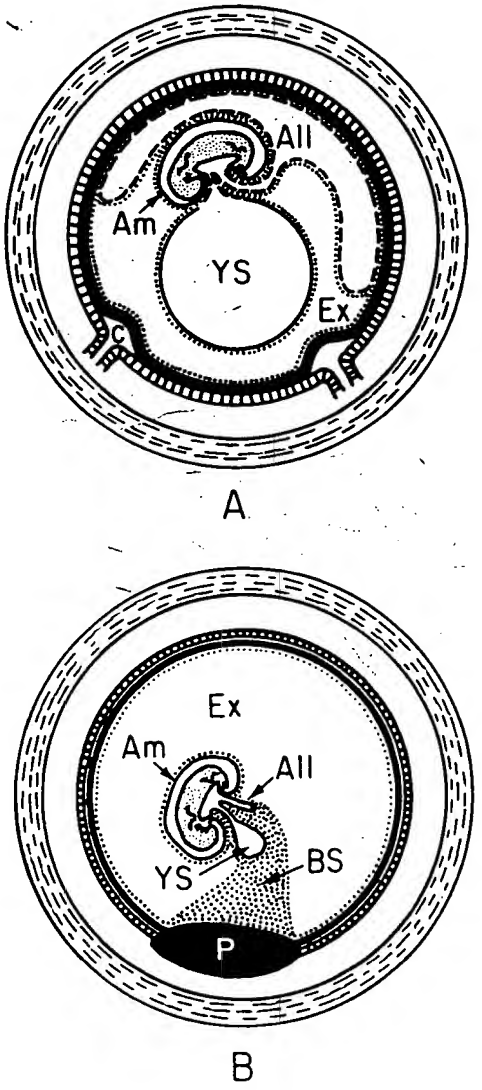

Fig. 25. Examples of different types of extraembryonic membrane configurations found among nonhuman primates. The amnion (Am) remains essentially the same in all species, but the allantois (All), which is large in *Galago* (A) and most other prosimians, is rudimentary in higher primates (B). YS, yolk sac; Ex, exocoelom; BS, body stalk; C, chorionic vesicle; P, placenta. (From Hendrickx and Houston, 1971).

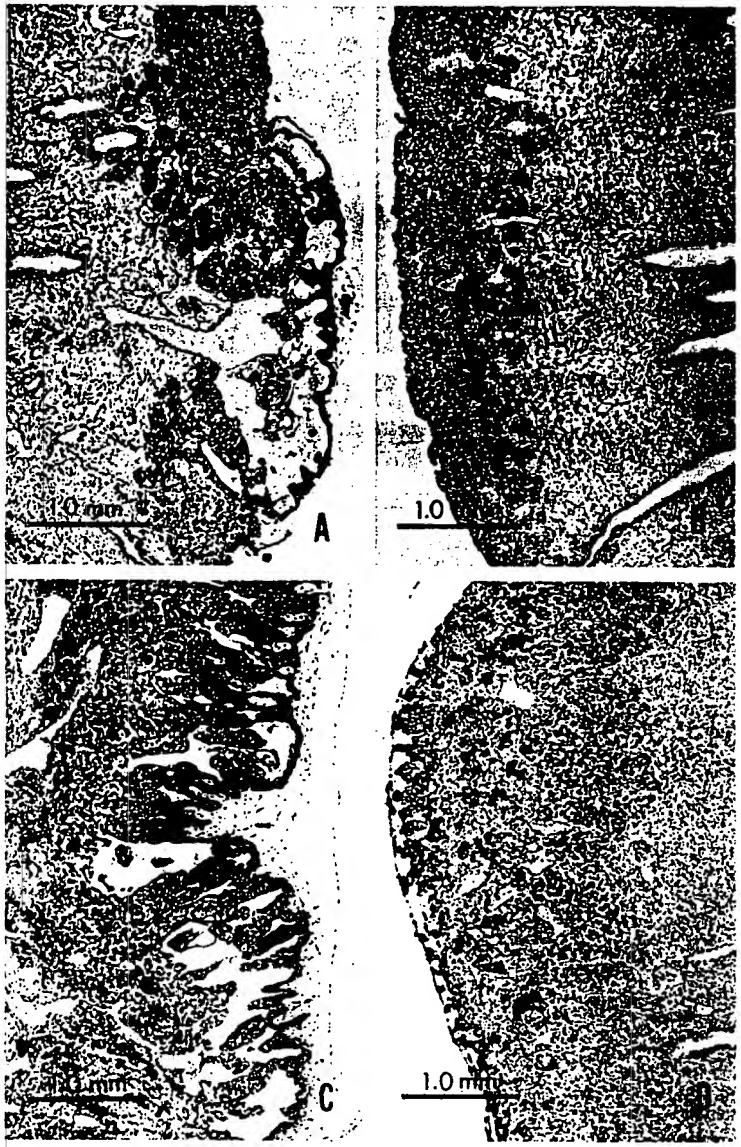

Fig. 26. Development of the placenta. The primary and secondary placental sites are shown for a 14-day-old embryo (A and B) and for a 17-day-old embryo (C and D). (A) Villi have not yet formed at 14 days but there is a broad communication between maternal blood channels and lacunae at the primary site. (B) Proliferative epithelium characterizes the secondary site. (C) Definitive villi with incomplete vascularization separated by lacunae (intervillous spaces) characterize the primary placenta at 17 days. (D) The villi at the secondary site are less advanced, lacking central stroma. A junctional zone, a necrotic area between the maternal and fetal tissues, is evident at both sites (from Wislocki and Streeter, 1938).

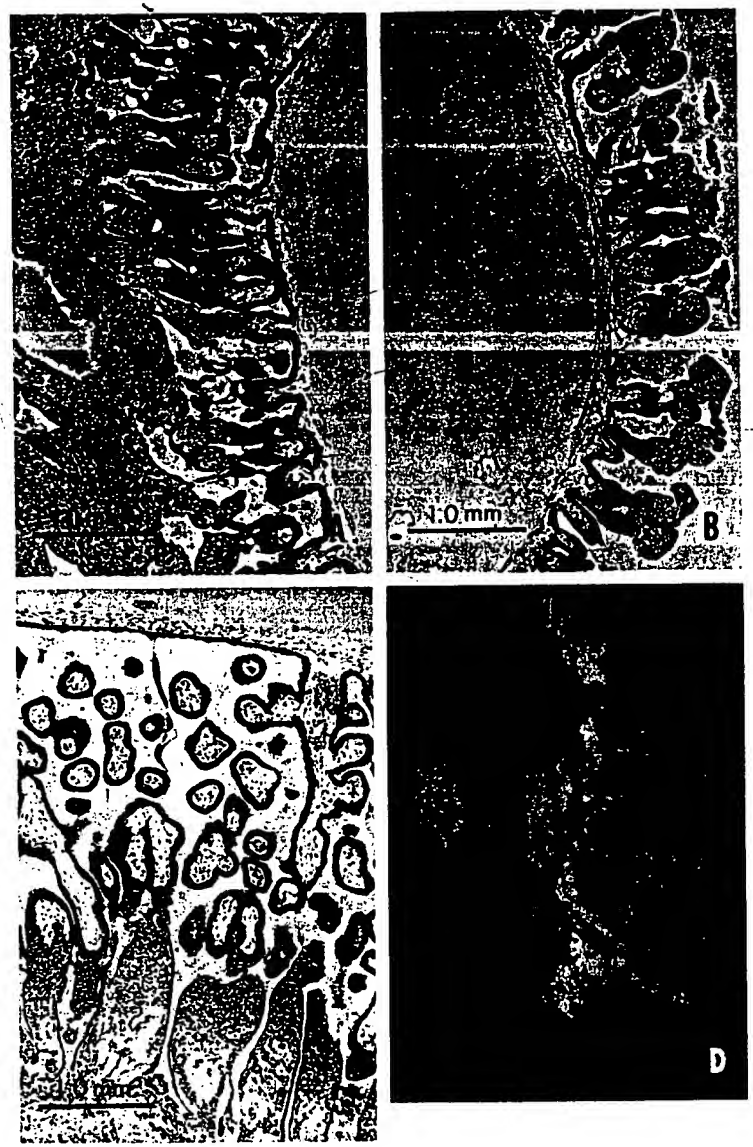

Fig. 27. Development of the placenta. The primary and secondary placenta of a 19½ day embryo are shown in (A) and (B), respectively. Branched villi are present in the primary placenta and the chorionic membrane is well vascularized. The villi of the secondary placenta (B) contains stroma. (C) Primary placenta from a 29-day embryo which is approaching the definitive stage. Trophoblastic cell columns extend to the necrotic zone. The villi are intricately branched and well vascularized. (D) Primary and secondary placental sites of a 19-day embryo showing the membranous chorion extended between the placental discs (from Wislocki and Streeter, 1938).

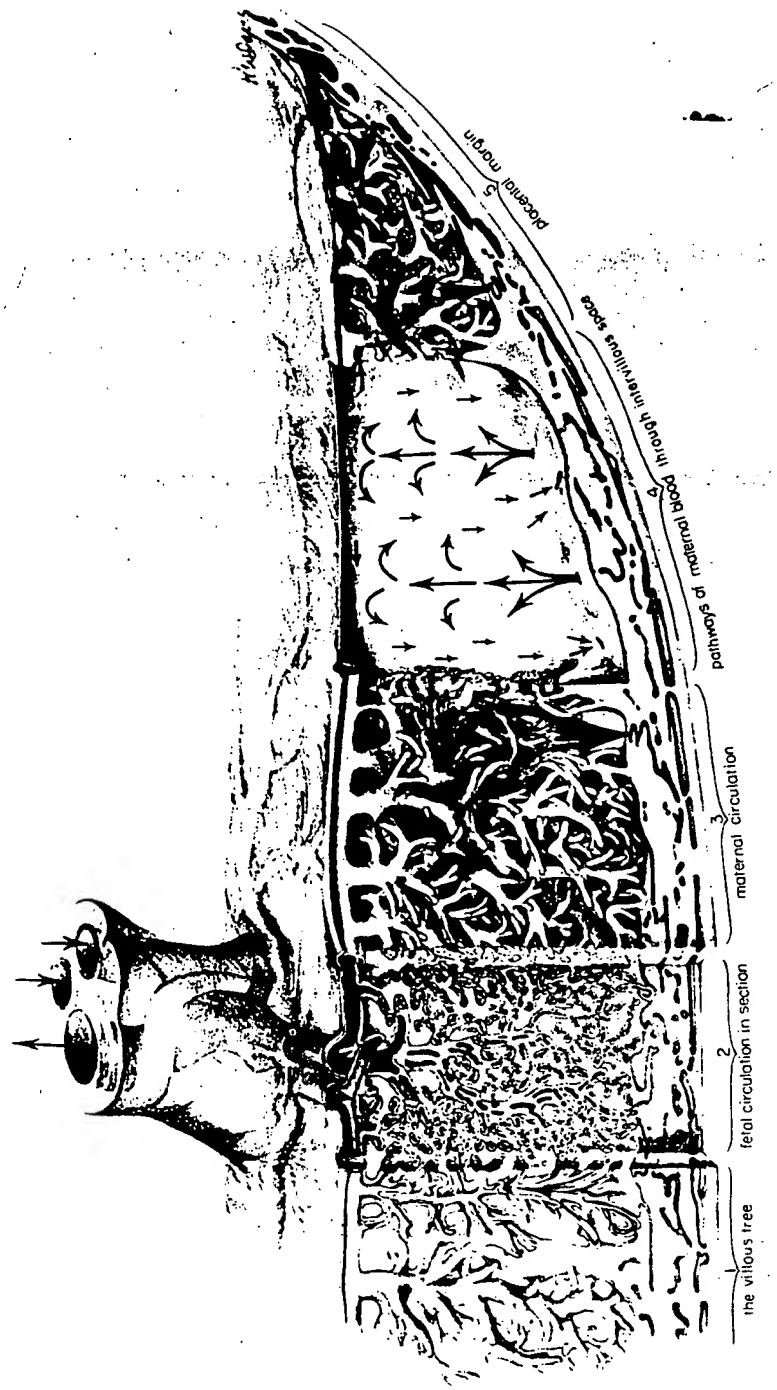

Fig. 28. A composite drawing of the hemochorial placenta (of a man or monkey) to show its structure and circulation. Drawn by Ranice W. Davis (from Ramsey, National Foundation Reprint Series, Courtesy of Carnegie Institute of Washington).

REFERENCES

Asling, C. W. and van Wagenen, G. (1967). *Arch. Oral Biol.* **12**, 909–910.
Blandau, R. J. (1972). *Acta Endocrinol. Suppl.* **166**, 69–92.
Dukelow, W. R. and Chernoff, H. N. (1969). *Amer. J. Physiol.* **216**, 682–686.
Enders, A. C. (1965). *Amer. J. Anat.* **116**, 29–68.
Harris, J. W. S. and Ramsey, E. M. (1966). *Contrib. Embryol. Carnegie Inst.* **38**, 45–48.
Hartman, C. G. (1932). *Contrib. Embryol. Carnegie Inst.* **23**, 1–161.
Hartman, C. G. (1933). *Amer. J. Obstet. Gynecol.* **26**, 600–608.
Hendrickx, A. G. (1972a). *Acta Endocrinol. Suppl.* **166**, 103–130.
Hendrickx, A. G. (1972b). "Medical Primatology, 1972" (E. I. Goldsmith and J. Moor-Jankowski, eds.), pp. 259–269. Karger, Basel.
Hendrickx, A. G. and Houston, M. L. (1971). *In* "Comparative Reproduction of Non-human Primates" (E. S. E. Hafez, ed.), pp. 334–381. Thomas, Springfield, Illinois.
Hertig, A. T., Rock, J., and Adams, E. C. (1956). *Amer. J. Anat.* **98**, 435–493.
Heuser, C. H. and Streeter, G. L. (1941). *Contrib. Embryol. Carnegie Inst.* **29**, 15–55.
Hill, J. P. (1932). *Phil. Trans. Roy. Soc. London* **B,221**, 45–178.
Houston, M. (1969). *Amer. J. Anat.* **126**, 1–16.
Kerr, G. R., Kennan, A. L., Waisman, H. A., and Allen, J. R. (1969). *Growth* **33**, 201–213.
Lewis, W. H. and Hartman, C. G. (1933). *Contrib. Embryol. Carnegie Inst.* **24**, 187–201.
Lewis, W. H. and Hartman, C. G. (1941). *Contrib. Embryol. Carnegie Inst.* **29**, 7–14.
Langman, J. (1969). "Medical Embryology." Williams & Wilkins, Baltimore, Maryland.
Luckett, W. P. (1970). *Anat. Rec.* **157**, 141–164.
Luckett, W. P. (1971). *Anat. Rec.* **169**, 369 (Abstr).
Marston, J. H. and Kelly, W. A. (1968). *Nature (London)* **217**, 1073–1074.
Mastroianni, L. and Brackett, B. G. (1972). *Acta Endocrinol. Suppl.* **166**, 48–58.
Meyer, R. K., Wolf, R. C., and Arslan, M. (1968). *Proc. 2nd Int. Congr. Primatol., Atlanta, 1968* Vol. 2, pp. 30–35, Karger, Basel.
Nishimura, H., Takano, K., Tanimura, T., and Yasudo, M. (1968). *Teratology* **1**, 281–290.
O'Rahilly, R. (1972). *Anat. Anz.* **130**, 556–559.
O'Rahilly, R. (1973). *Carnegie Inst. Wash. Publ.* 631.
Panigel, M. (1970). *C.R. Ass. Anat.* **145**, 319–337.
Rakic, P. (1974). *Science* **183**, 425–427.
Ramsey, E. M. and Harris, J. W. S. (1966). *Contrib. Embryol. Carnegie Inst.* **38**, 59–70.
Stambaugh, R. and Buckley, J. (1970). *Biol. Reprod.* **3**, 275–282.
Stambaugh, R. and Buckley, J. (1972). *Fert. Steril.* **23**, 348–352.
Starck, D. (1956). *In* "Primatologiae" (A. H. Schultz and D. Starck, eds.), Vol. 1, pp. 723–886. Karger, Basel.
Steffek, A. J., Verrusio, A. C., and King, C. T. E. (1968). *Teratology* **1**, 425–430.
Strauss, F. (1945). *Rev. Suisse Zool.* **52**, 213.
Streeter, G. L. (1942). *Contrib. Embryol. Carnegie Inst.* **30**, 211–245.
Streeter, G. L. (1945). *Contrib. Embryol. Carnegie Inst.* **31**, 29–63.
Streeter, G. L. (1948). *Contrib. Embryol. Carnegie Inst.* **32**, 133–203.
Streeter, G. L. (1951). *Contrib. Embryol. Carnegie Inst.* **34**, 165–196.
Suzuki, S. and Mastroianni, L. (1968). *Fert. Steril.* **19**, 500–508.
van Wagenen, G. and Simpson, M. (1965). "Embryology of the Ovary and Testis Homo sapiens and Macaca mulatta." Yale Univ. Press, New Haven, Connecticut.
Wilson, J. G. (1972). *Acta Endocrinol. Suppl.* **166**, 261–292.
Wilson, J. G. and Gavan, J. A. (1967). *Anat. Rec.* **158**, 99–110.
Wilson, J. G., Fradkin, R., and Hardman, A. (1970). *Teratology* **3**, 59–71.
Wislocki, G. B. and Streeter, G. L. (1938). *Contrib. Embryol. Carnegie Inst.* **27**, 1–66.